

Amendments to the Specification:

Insert the paper copy of the Sequence Listing filed herewith following the Oath/Declaration.

Please replace the paragraph beginning at page 3, line 13 with the following amended paragraph:

In one aspect, the invention features an isolated polypeptide that includes a polypeptide having the sequence X1-R-X2-R-X3, wherein X1, X2 and X3 are any amino acid and polynucleotides encoding such polypeptides. The polypeptide can have at least seven amino acids. The invention also features an isolated polypeptide selected from the group consisting of: GYRQRLE (SEQ ID NO:1), EYRYRSV (SEQ ID NO:2), GQRARIS (SEQ ID NO:3) and QARRRQS (SEQ ID NO:4), and polynucleotides encoding such polypeptides. Polypeptides of the invention further can include a pharmaceutical formulation.

Please replace the paragraph beginning at page 4, line 11, with the following amended paragraph:

The invention also features a method for treating a subject having cystic fibrosis. The method includes administering to the subject a pharmaceutical formulation comprising a polypeptide having an R-X-R sequence in an amount effective for treating cystic fibrosis. In one embodiment, the X amino acid of the R-X-R sequence is not alanine, asparagine or glutamate. The polypeptide can have at least four amino acids, e.g., at least seven amino acids. The polypeptide can be selected from the group consisting of: GYRQRLE (SEQ ID NO:1), EYRYRSV (SEQ ID NO:2), GQRARIS (SEQ ID NO:3) and QARRRQS (SEQ ID NO:4).

Please replace the paragraph beginning at page 4, line 24, with the following amended paragraph:

In another aspect, the invention features a method for treating a subject having or suspected of having a physiological disorder associated with an export-incompetent protein. The method includes administering to the subject a pharmaceutical formulation comprising a polypeptide having an R-X-R sequence in an amount effective for treating a physiological

disorder associated with an export-incompetent protein. The physiological disorder or condition can be selected from the group consisting of: macular dystrophy and Stargardt's disease. The export-incompetent protein can be selected from the group consisting of: ion channels, ABC proteins, growth factors, immune regulators, adhesion proteins, hormones, clotting factors, hemostatic regulators and receptors thereof. In one embodiment, the X amino acid of the R-X-R sequence is not alanine, asparagine or glutamate. The polypeptide can have at least four amino acids, e.g., at least seven amino acids. The polypeptide can be selected from the group consisting of: GYRQRLE (SEQ ID NO:1), EYRYRSV (SEQ ID NO:2), GQRARIS (SEQ ID NO:3) and QARRRQS (SEQ ID NO:4).

Please replace the paragraph beginning at page 5, line 12, with the following amended paragraph:

A method for identifying an agent that inhibits or disrupts an interaction between an R-X-R polypeptide and an ER retention factor also is described. The method includes incubating a polypeptide having an R-X-R sequence and an ER retention factor under conditions allowing their interaction; adding a test agent to the incubation; and detecting binding between the polypeptide and the ER retention factor, where decreased binding in the presence of the test agent identifies an agent that inhibits or disrupts an interaction between an R-X-R polypeptide and an ER retention factor. The method can be performed in vitro. The polypeptide can have at least 4 amino acids. The X amino acid of the R-X-R sequence may not be alanine, asparagine or glutamate. The polypeptide can be selected from the group consisting of: GYRQRLE (SEQ ID NO:1), EYRYRSV (SEQ ID NO:2), GQRARIS (SEQ ID NO:3) and QARRRQS (SEQ ID NO:4).

Please replace the paragraph beginning at page 5, line 23, with the following amended paragraph:

The invention also features a method for identifying an ER retention factor. The method includes contacting a composition suspected of containing an ER retention factor with a polypeptide having an R-X-R sequence under conditions allowing interaction between the factor and the polypeptide; and detecting binding between the factor and the polypeptide, thereby

identifying an ER retention factor. The method can be performed in vitro. The polypeptide can have at least four amino acids, e.g., at least seven amino acids. The polypeptide can be selected from the group consisting of: GYRQRLE (SEQ ID NO:1), EYRYRSV (SEQ ID NO:2), GQRARIS (SEQ ID NO:3) and QARRRQS (SEQ ID NO:4).

Please replace the paragraph beginning at page 7, line 17, with the following amended paragraph:

Figure 6 is an amino acid sequence of human cystic fibrosis transmembrane conductance regulator (CFTR) (SEQ ID NO:5).

Please replace the paragraph beginning at page 15, line 3, with the following amended paragraph:

Exemplary polypeptides having an AFT sequence are heptamers based on the AFT sequence region of the corresponding CFTR polypeptide. In particular, GYRQRLE (SEQ ID NO:1), which is based on the sequence SWTRPILRKGYRQRLELSDIYQIPS (SEQ ID NO:6); EYRYRSV (SEQ ID NO:2), which is based on the sequence NIIFGVSYDEYRYRSVIKACQLEED (SEQ ID NO:7); GQRARIS (SEQ ID NO:3), which is based on the sequence GEGGITLSGGQRARISLARAVYKDA (SEQ ID NO:8); and QARRRQS (SEQ ID NO:4), which is based on the sequence SVISTGPTLQARRRQSVLNLMTHSV (SEQ ID NO:9). It is understood that the standard single letter amino acid abbreviation is used to denote the amino acids of the invention polypeptides (see for example, Zubay, G.L., Biochemistry page 12, Addison-Wesely Publishing, Inc., 1983).

Please replace the paragraph beginning at page 29, line 11, with the following amended paragraph:

The methods for treating a subject having a physiological disorder associated with an export incompetent protein can be practiced with the invention polypeptides having an AFT sequence based on the CFTR sequence, such as GYRQRLE (SEQ ID NO:1), EYRYRSV (SEQ ID NO:2), GQRARIS (SEQ ID NO:3) and QARRRQS (SEQ ID NO:4). Alternatively, the

methods can be practiced using polypeptides having AFT sequence, including flanking sequences, if desired, based upon the amino acid sequence of the export incompetent polypeptide that causes or is associated with the physiological disorder being treated. In this way, increased specificity can be provided by using polypeptides having an AFT polypeptides sequence based on the polypeptide sequence. Increased specificity may decrease potentially deleterious side effects caused by inducing or increasing ER export of unrelated polypeptides, for example, by inhibiting the interaction of an ER retention factor with the unrelated protein thereby increasing its export.

Please replace the paragraph beginning at page 33, line 4, with the following amended paragraph:

AFT polypeptides also can be employed to identify an ER retention factor. Thus, the invention further provides a method for identifying an ER retention factor. A method of the invention comprises contacting a composition suspected of containing an ER retention factor with a polypeptide having an R-X-R sequence under conditions allowing their interaction and detecting binding between the factor and the polypeptide, thereby identifying an ER retention factor. The method can be performed in vitro. The method also can employ polypeptides having various lengths as set forth herein. Specific polypeptides include GYRQRLE (SEQ ID NO:1), EYRYRSV (SEQ ID NO:2), GQRARIS (SEQ ID NO:3) and QARRRQS (SEQ ID NO:4).

Please replace the paragraph beginning at page 33, line 24, with the following amended paragraph:

In accordance with the present invention, there are provided kits for treating subjects having or suspected of having a physiological disorder or condition associated with an export-incompetent protein. A kit of the invention contains one or more AFTs or a polypeptide containing an AFT sequence, and a label or packaging insert for treating a physiological disorder associated with an export-incompetent protein as set forth herein in suitable packaging material. In various aspects, the kits contain R-X-R tripeptides, preferably polypeptides having an R-X-R sequence at least 4 amino acids long, more preferably polypeptides having an R-X-R sequence at least 5 amino acids long, and most preferably polypeptides having R-X-R sequence at least 6

amino acids or longer. It is understood that any invention polypeptide can be included in the kits of the invention. Particular embodiments include peptides having the sequences GYRQRLE (SEQ ID NO:1), EYRYRSV (SEQ ID NO:2), GQRARIS (SEQ ID NO:3) and QARRRQS (SEQ ID NO:4).

Please replace the paragraph beginning at page 35, line 22, with the following amended paragraph:

Each of the arginine to lysine substitutions were introduced into plasmids containing either the wild-type or Δ F508 CFTR sequences. Briefly, a full-length human CFTR cDNA in pNUT vector (Chang, X.-B. et al. (1993). *J. Biol. Chem.* 268:11304-11311) was utilized as a template for site-directed mutagenesis (QuickChange Site Directed Mutagenesis Kit, Stratagene, La Jolla, CA) by polymerase chain reaction (PCR) according to the manufacturer's recommendation. The following oligonucleotides were used to introduce R29K, R516K, R555K and R766K into wild-type CFTR cDNA. R29K:

CAATTTTGAGGAAAGGATACAAACAGCGCCTGGAATTGTCAG (SEQ ID NO:10) and CTGACAATTCCAGGCGCTGTTTGTATCCTTTCCTCAAAATTG (SEQ ID NO:11); R516K: CCTATGATGAATATAAATACAGAAGCCTCATC (SEQ ID NO:12) and GATGACGCTTCTGTATTTATATTCATCATAGG (SEQ ID NO:13); R555K: GGAGGTCAACGAGCAAAAATTTCTTTAGCAAGAG (SEQ ID NO:14) and CTCTTGCTAAAGAAATTTTTGCTCGTTGACCTCC (SEQ ID NO:15); R766K: CTTCAGGCACGAAGGAAGCAGTCTCTCCTGAACC (SEQ ID NO:16) and GGTTCAGGACAGACTGCTTCCTTCGTGCTGAAG (SEQ ID NO:17). To combine four lysine substitutions in one cDNA, the following fragments were prepared: Dra III - Kpn I fragment which contains part of wild-type CFTR cDNA from nt 3328 to 4721 and most of the pNUT expression vector; Kpn I - Afl II fragment which contains part of the pNUT expression vector and part of CFTR from nt 72 to 993 covering the R29K mutation; Afl II - Dra III fragment from nt 994 to 1777 covering the R516K substitution; Dra III - EcoR I fragment from nt 1778 to 2230 covering the R555K substitution; and EcoR I - Dra III fragment from nt 2231 to 3327 covering the R766K substitution. These five fragments were ligated together to generate full length CFTR cDNA in pNUT (T4 DNA ligase, New England Biolabs, Beverly, MA). The

sequences of the four fragments covering these substitutions were verified after insertion into the pNUT-CFTR. To combine the cystic fibrosis causing mutation, $\Delta F508$, with each individual or all four of the above substitutions, the same strategy was utilized, except that pNUT- $\Delta F508$ CFTR was utilized as template. pNUT- $\Delta F508$ CFTR/R29K was made by ligating the following three fragments together, Kpn I - Afl II fragment which contains part of pNUT vector and part of CFTR from nt 72 to 993 covering the R29K substitution, Afl II - Hpa I fragment from nt 994 to 2463 covering the $\Delta F508$ substitution, and Hpa I - Kpn I fragment which contains the part of CFTR from nt 2464 to 4721 and part of the pNUT vector. The sequences covering $\Delta F508$, R29K, R516K, R555K and R766K were verified after insertion into the expression vector pNUT.